Analysis of Terminal Deletions using a Generalized Time-Dependent Model of Radiation-Induced Formation of Chromosomal Aberrations

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We have developed a model that can simulate different types of radiation induced chromosomal aberrations (CA's) and can provide predictions on the frequency and size of chromosomes with terminal deletions. Chromosomes with terminal deletions lack telomeres and this can elicit sister chromatid unions and the prolonged breakage/fusion/bridge (B/F/B) cycles that have been observed in mammalian tumors. The loss of a single telomere has been shown to cause extensive genomic instability through the B/F/B cycle process. Our model uses a stochastic process of DNA broken end joining, in which a realistic spectrum of CA's is created from improperly joined DNA free ends formed by DNA double strand breaks (DSBs). The distribution of the DNA free ends is given by a mechanistic model that takes into account the chromatin structure and track structure for high-LET radiation. The model allows for DSB clustering from high-LET radiation and simulates the formation of CA's in stages that correspond to the actual time after radiation exposure. The time scale for CA formation is derived from experimental data on DSB repair kinetics. At any given time a nucleus may have intact chromosomes, CA's, and/or unrepaired fragments, some of which are defined as terminal deletions, if they are capped by one telomere. The model produces a spectrum of terminal deletions with their corresponding probabilities and size distributions for different heavy ions exposures for the first division after exposure. This data provides valuable information because there is limited experimental data available in the literature on the on the actual size of terminal deletions. We compare our model output to the available experimental data and make a reasonable extrapolation on the number of chromosomes lacking telomeres in human lymphocytes exposed to heavy ions. This model generates data which may lead to predictions on the rate of genomic instability in cells after exposure to high charge and energy nuclei affecting astronauts during space missions.